

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Loco-Regional Recurrence

Loco-regional Recurrence

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- **Versionen 2002–2017:**
**Audretsch / Bauerfeind / Brunnert / Budach /
Costa / Dall / Fehm / Fersis / Friedrich / Harbeck /
Gerber / Göhring / Hanf / Lisboa / Maass /
Mundhenke / Rezai / Simon / Solomayer /
Souchon / Thomssen / Wenz / Bauerfeind /Thomssen**
- **Version 2018:**
Kühn / Friedrich

Loco-regional Recurrence Incidence and Prognosis

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Localization	Frequency (%)	5-y. Overall Survival (%)
Ipsilateral recurrence¹ (post BOT + irradiation)	10 (2–20)	65 (45–79)
Chest wall¹ (post mastectomy)	4 (2–20)	50 (24–78)
As above plus supraclavicular fossa²		
Axilla:	34%	49% (3-y. OS)
After ALND¹	1 (0.1–8)	55 (31–77)
After SNB⁴	1	93%
Multiple localizations²	16 (8–19)	21 (18–23)

¹ Haffty et al. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991;

² Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 201;

³ Karabali-Dalamaga S et al. Br Med J 2(6139):730-733,1978;

⁴ Andersson Y, et al. Br J Surg 99(2):226-31,2012

Loco-regional Recurrence Staging

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Oxford		
LoE	GR	AGO

Examinations before treatment

■ Tissue biopsy	5	D	++
■ Re-assessment of ER, PgR, HER2	3b	B	++
■ Complete re-staging	5	D	++

Risk Factors for Loco-Regional Recurrence at Primary Diagnosis

**Oxford
LoE**

Increased risk for loco-regional recurrence

- | | |
|---|-----|
| ▪ Young age | 1a |
| ▪ Positive microscopic margins (R1) of the primary tumor | 1a |
| ▪ Omitting adjuvant radiotherapy (if indicated) | 1a |
| ▪ Extensive intraductal component | 1b |
| ▪ Vessel invasion | 1b |
| ▪ HER2 positive and triple negative > Luminal B-like > luminal A-like | 2a |
| ▪ Number of involved lymph nodes | 1a |
| ▪ Grading (G3) | 1b* |
| ▪ Elevated proliferation markers: e.g. Ki67; | 2b |
| ▪ pT (> 2) | 1b* |
| * nodal negativ | 1a |
| ▪ Inflammatory breast cancer | 2b |
| ▪ Medial tumor localisation | 4 |
| ▪ Obesity (Body mass index) | 1a |

Metaanalysis: TNBC and Local Recurrence

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Wang et al, Surg Oncol. 2013 Dec;22(4):247-55.

n = 15312 BC-patients, 22 studies, Hazard-ratios

BCT	vs.	ME
ILRR	0.75 (0.65-0.87)	
DM	0.68 (0.60-0.76)	

TNBC-subtype	vs.	other subtype
ILRR	1.88 (1.58-2.22)	
DM	2.12 (1.72-2.62)	

TNBC-subtype	vs.	HER2-subtype
ILRR	0.69 (0.53-0.91)	
DM	n.s.	

ILRR: ipsilateral locoregional recurrence

DM: distant metastasis

TNBC: triple negative breast cancer

BCT: breast conserving therapy

ME: mastectomy

Risk Factors for Locoregional Recurrences after ME

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Karlsson et al. Ann Oncol 23:2852-8, 2012

IBCSG-study, 13 randomized trials, n= 8106 patients

Risk factors for 10 yr. cumulative incidence ...:

- | | |
|--------------------------------------|--|
| ... > 15% chest wall | age < 40; ≥ 4 pos. nodes,
0-7 uninvolved nodes |
| ... > 10% supraclavicular: | ≥ 4 pos. nodes |
| ... > 5% axillary failure: | age < 40; unknown tumor size,
0-7 uninvolved nodes |

Metaanalysis: 7174 BET and 5418 ME

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Lowery AJ, et al. Breast Cancer Res Treat 133(3):831-41, 2012

After BCT:

HR-positive tumors show a lower risk for LRR than...

triple negative tumors (RR 0.38) and....

HER2-expressing tumors (RR 0.34)*

After ME:

HR-positive tumors show a lower risk for LRR than...

HER2-expressing tumors (RR 0.69)* and...

triple negative tumors (RR 0.61)

Result:

HR-positive tumors exhibit the lowest rate of local recurrence.

* most pts. were treated in the time before routine adjuvant trastuzumab use

Loco-regional Recurrence Prognostic / Predictive factors

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Parameters of the locally recurrent tumor to define the risk for re-recurrence

- Tumor size
- Multifocality
- Localisation
- Negative progesterone receptor

Parameters of the locally recurrent tumor to define the risk for distant metastasis/survival

- Early (< 2-3 yrs.) vs. late recurrence
- LVI / Grade / ER-neg / positive margins
(if ≥ 2 factors positive)

Predictive factors for treatment considerations

- HER2
- ER and PgR

	Oxford		
	LoE	GR	AGO
Tumor size	2a	B	
Multifocality	2a	B	
Localisation	2b	B	
Negative progesterone receptor	3b	B	
Early (< 2-3 yrs.) vs. late recurrence	2b	B	
LVI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)	3b	B	
HER2	2b	B	++
ER and PgR	2b	B	++

Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence

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Panet-Raymond V et al. Cancer 117:2035, 2011

n = 6020 pts., retrospective cohort-study
pT1/2, N0 tumors, breast conserving treatment
269 ipsilateral breast tumor recurrences (IBTR)

Multivariate analysis:

TTR < 48 months

LVSI (of the LRR)

ER negative LR-tumor

high grade

close margins of recurrent tumor

→ if ≥ 2 factors positive \Rightarrow worse OS

Ipsilateral Recurrence after BCT Surgery

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- Mastectomy (aim: R0)
- Re-BCS with tumor-free margins (R0)
- Axillary intervention after prior AxDissection if cN0
- SLNE after prior SLNE if cN0*
- Palliative surgery in M1-situation
(e.g. pain, ulceration, psychosocial indication)

Oxford		
LoE	GR	AGO
3b	B	++
3	C	+/-
4	C	-
2a	B	-
5	D	+

* If no sentinel lymph node can be identified, axillary dissection is not recommended;
no operation outside the ipsilateral axilla is recommended

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence - Surgery

- **Curative situation: R0-resection**
- **Palliative situation: Resection of deep parts of the chest wall**
- **Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)**

Oxford		
LoE	GR	AGO
2b	A	++
5	D	+/-
5	D	+

Loco-regional Recurrence after R0-Resection Systemic Treatment

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	Oxford		
	LoE	GR	AGO
<p>According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)</p> <ul style="list-style-type: none"> ▪ Endocrine therapy in endocrine responsive tumors ▪ Chemotherapy (consider preoperative) ▪ In case of HER2 positive disease, chemotherapy + HER2 targeted therapy 	2b	B	++
	2b	B	+
	5	D	+

Chemo Therapy by Loco-regional Recurrence

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■ CALOR Trial update

n = 163 (2003-2010), median follow-up of 4.9 years, all R0 resection
5-year disease-free survival: 69% (95% CI 56-79) with chemotherapy
vs. 57% (44-67) without chemotherapy (hazard ratio 0.59
[95% CI 0.35-0.99]; p=0.046): 24 (28%) patients vs. 34 (44%).

Adjuvant chemotherapy was significantly more effective in
ER negative disease ($p_{\text{interaction}}=0.046$).

Chemotherapie bei lokoregionärem Rezidiv

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■ CALOR Trial update

Endpoint	ER-positive			ER-negative		
	CT	No-CT	HR (95%CI)	CT	No-CT	HR (95%CI)
10-yr DFS	50%	59%	1.07 (0.57 – 2.00)	70%	34%	0.29 (0.13 – 0.67)
Interaction P-Value =0.013						
10-yr OS	76%	66%	0.70 (0.32 – 1.55)	73%	53%	0.48 (0.19 – 1.20)
Interaction P-value =0.53						
10-yr BCFI	58%	62%	0.94 (0.47 – 0.85)	70%	34%	0.29 (0.13 – 0.67)
Interaction P-value = 0.034						

Locoregional Recurrence in Case of R1-Resection/Inoperability – Systemic Treatment

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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Endocrine therapy in endocrine responsive tumors 	2b	B	++
<ul style="list-style-type: none"> Chemotherapy (pre- or postoperatively) 	2b	B	+
<ul style="list-style-type: none"> HER2-targeted therapy in HER2-positive tumors (with chemotherapy) 	5	D	++

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

- Endocrine therapy in endocrine responsive tumors
- Chemotherapy (pre- or postoperatively)
- HER2-targeted therapy in HER2-positive tumors (with chemotherapy)

Ipsilateral Recurrence after BCT Radiotherapy

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After Re-BCS

- Whole breast irradiation
(in case adjuvant radiotherapy was not performed)
- Re-breast irradiation (Partial breast radiation,
brachytherapy, external beam RT)

After mastectomy

- Radiation of chest wall +/- regional lymph nodes
(14% involved supraclavicular metastasis)
- Radiation dose escalation (+10%)
- Repeated irradiation (e.g. as brachytherapy)
with hyperthermia

	Oxford		
	LoE	GR	AGO
■ Whole breast irradiation (in case adjuvant radiotherapy was not performed)	3b	C	++
■ Re-breast irradiation (Partial breast radiation, brachytherapy, external beam RT)	3b	C	+/-
■ Radiation of chest wall +/- regional lymph nodes (14% involved supraclavicular metastasis)	2b	B	+/-
■ Radiation dose escalation (+10%)	3b	C	-
■ Repeated irradiation (e.g. as brachytherapy) with hyperthermia	3a	C	+/-

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Radiotherapy

Oxford		
LoE	GR	AGO

Chest-Wall Recurrence (R0-Resection) after Mastectomy

- If no prior postmastectomy radiotherapy
 - Curative situation:
irradiation of the chest wall +/- regional lymph nodes
- Re-irradiation (chest wall + hyperthermia)

2b	B	+
1b	B	+/-

Axillary Recurrence

- Irradiation of axilla after R0-surgery
 - No prior adjuvant irradiation of the axilla
 - Adjuvant irradiation of the axilla

3b	C	+
5	D	+/-

Loco-Regional Recurrence

Treatment Options in Non Curative Cases

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- **Concomitant radio-chemotherapy**
- **Hyperthermia (in centers listed on DKG website)**
 - In combination with radiotherapy
 - In combination with chemotherapy
- **Intra-arterial chemotherapy**
- **Photodynamic therapy**
- **Electrochemotherapy**

Oxford		
LoE	GR	AGO
3b	C	+
1b	B	+
1b	C	+/-
4	C	+/-
4	C	+/-
4	C	+/-
3b	C	+/-